

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVENTIS PHARMA S.A.,)	
)	
Plaintiff,)	Civil Action No. 06-636-GMS
)	
v.)	
)	
BAXTER HEALTHCARE CORP.,)	
)	
Defendant.)	
)	
)	
BAXTER HEALTHCARE CORP.,)	
)	
Counterclaimant,)	
)	
v.)	
)	
AVENTIS PHARMA S.A.,)	
)	
Counterdefendant.)	

AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Aventis Pharma S.A. (“Aventis Pharma”), for its Amended Complaint against Defendant Baxter Healthcare Corp. (“Baxter”), hereby states as follows.

NATURE OF THE ACTION

1. This is an action for infringement of United States Patent No. 5,565,427 (“the ‘427 patent”), arising under the patent laws of the United States, 35 U.S.C. § 100 *et seq.* This action relates to Baxter’s making, using, offering for sale, selling and importing into the United States of its 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU dosage strength ADVATE® products, which contain a stabilized solution with Factor VIII:C activity.

2. On April 11, 2003, A. Nattermann & Cie GmbH (“Nattermann”) and Aventis Behring L.L.C. (“Aventis Behring”) filed suit against Baxter in this Court, seeking a declaratory

judgment that Baxter's imminent and intended manufacture, use, offering for sale, selling or importing into the United States of its ADVATE® product would constitute infringement of the '427 patent. During discovery, Baxter produced certain information that it had refused to provide absent litigation. Nattermann, the owner of the '427 patent at that time, provided this new information to the U.S. Patent and Trademark Office ("PTO") and requested that the PTO reexamine the '427 patent in view of this information. Due to the reexamination, the parties stipulated to a dismissal of the litigation without prejudice, which the Court entered on November 4, 2003. In that stipulation, the parties agreed to re-file the action in this same Court once the PTO completed its reexamination of the '427 patent. The reexamination process is now over, and, accordingly, Aventis Pharma brings the present action.

THE PARTIES

3. Aventis Pharma is a corporation organized under the laws of France with its corporate headquarters at 20, avenue Raymond Aron, 92160 Antony, France.

4. Upon information and belief, Baxter is a Delaware Corporation having its corporate offices at One Baxter Parkway, Deerfield, Illinois 60015.

JURISDICTION AND VENUE

5. This Court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

6. This Court has jurisdiction over Baxter because, on information and belief, Baxter is a Delaware corporation and purposefully has conducted and continues to conduct business in this judicial district, has placed the infringing ADVATE® products in the stream of commerce knowing and intending that this judicial district was and is a likely destination of those products, has caused injury to Aventis Pharma in this judicial district, and has committed acts of

infringement in this judicial district. In addition, Baxter stipulated to the Court's jurisdiction over this matter in the prior related action.

7. Upon information and belief, this Court has personal jurisdiction over Baxter. Indeed, Baxter stipulated to this Court's exercise of personal jurisdiction over Baxter in the prior related action.

8. Upon information and belief, venue is proper in this judicial district under 28 U.S.C. §§ 1391(c) and 1400(b). Indeed, Baxter stipulated to venue in the prior related action.

FIRST COUNT FOR PATENT INFRINGEMENT

9. The PTO duly and legally issued the '427 patent, entitled "Stabilized Factor VIII Preparations," to Behringwerke Aktiengesellschaft, as assignee of inventor Wilfried Freudenberg, on October 15, 1996. A true and correct copy of the '427 patent is attached as Exhibit A.

10. Behringwerke Aktiengesellschaft merged with Hoechst Aktiengesellschaft, and Hoechst Aktiengesellschaft subsequently assigned the '427 patent to Centeon Pharma GmbH, which in turn became Aventis Behring GmbH upon the merger of Hoechst and Rhone Poulenc to form Aventis. Aventis Behring GmbH subsequently assigned the rights to the '427 patent to Nattermann.

11. Aventis Pharma is the present owner of the '427 patent as a result of an assignment from Nattermann.

12. On July 23, 2002, the PTO issued a first Reexamination Certificate. A true and correct copy of the first Reexamination Certificate is attached as Exhibit B.

13. On October 10, 2006, the PTO issued a second Reexamination Certificate. A true and correct copy of the second Reexamination Certificate is attached as Exhibit C.

14. The '427 patent discloses and claims, *inter alia*, stabilized solutions with factor VIII:C activity and methods of manufacturing such stabilized solutions.

15. Baxter has knowledge of the '427 patent and of the infringement allegations regarding Baxter's ADVATE® products as a result of the earlier action and the events preceding that action.

16. Based on information available from the United States Food and Drug Administration's ("FDA") Web site (www.fda.gov), the FDA granted Baxter approval on July 25, 2003, to manufacture, use, offer to sell and sell in the United States its 250 IU, 500 IU, 1000 IU, and 1500 IU dosage strength products under the trademark ADVATE®.

17. On information and belief, Baxter began selling and offering for sale its 250 IU, 500 IU, 1000 IU and 1500 IU dosage strength ADVATE® products in this judicial district and elsewhere in the United States in August of 2003.

18. Baxter's making, using, offering for sale, selling and importing into the United States of its 250 IU, 500 IU, 1000 IU, and 1500 IU dosage strength ADVATE® products infringe one or more claims of the '427 patent under 35 U.S.C. § 271.

19. On information and belief, the FDA granted Baxter approval on May 9, 2006, to manufacture, use, offer to sell and sell in the United States its 2000 IU dosage strength ADVATE® product. *See* Exhibit D.

20. On information and belief, Baxter began selling and offering for sale its 2000 IU dosage strength ADVATE® product in this judicial district and elsewhere in the United States in May of 2006. *See* Exhibit D.

21. Baxter's making, using, offering for sale, selling and importing into the United States of its 2000 IU dosage strength ADVATE® product infringes one or more claims of the '427 patent under 35 U.S.C. § 271.

22. On information and belief, the FDA granted Baxter approval on July 10, 2007, to manufacture, use, offer to sell and sell in the United States its 3000 IU dosage strength ADVATE® product. *See* Exhibit E.

23. On information and belief, Baxter began selling and offering for sale its 3000 IU dosage strength ADVATE® product in this judicial district and elsewhere in the United States in August of 2007. *See* Exhibit E.

24. Baxter's making, using, offering for sale, selling and importing into the United States of its 3000 IU dosage strength ADVATE® product infringes one or more claims of the '427 patent under 35 U.S.C. § 271.

DAMAGES AND OTHER HARM SUFFERED BY AVENTIS PHARMA

25. Baxter's acts of infringement have damaged Aventis Pharma in an amount not yet determined and will continue to damage Aventis Pharma in the future.

26. Upon information and belief, Baxter's acts of infringement constitute willful infringement, entitling Aventis Pharma to treble damages and attorneys' fees.

PRAYER FOR RELIEF

WHEREFORE, Aventis Pharma respectfully requests that the Court enter judgment in its favor, and against Baxter, on the patent infringement claim set forth above, and that it award the following relief:

- (1) find that Baxter infringes at least one claim of the '427 patent by its making, using, offering for sale, selling and importing into the United States of its 250 IU dosage strength ADVATE® product;
- (2) find that Baxter infringes at least one claim of the '427 patent by its making, using, offering for sale, selling and importing into the United States of its 500 IU dosage strength ADVATE® product;
- (3) find that Baxter infringes at least one claim of the '427 patent by its making, using, offering for sale, selling and importing into the United States of its 1000 IU dosage strength ADVATE® product;
- (4) find that Baxter infringes at least one claim of the '427 patent by its making, using, offering for sale, selling and importing into the United States of its 1500 IU dosage strength ADVATE® product;
- (5) find that Baxter infringes at least one claim of the '427 patent by its making, using, offering for sale, selling and importing into the United States of its 2000 IU dosage strength ADVATE® product;
- (6) find that Baxter infringes at least one claim of the '427 patent by its making, using, offering for sale, selling and importing into the United States of its 3000 IU dosage strength ADVATE® product;
- (7) find that Baxter's infringement has been willful;
- (8) award Aventis Pharma damages adequate to compensate it for the aforesaid infringement, together with prejudgment interest thereon;
- (9) treble damages under 35 U.S.C. § 284 because of Baxter's willful infringement;

- (10) award Aventis Pharma its reasonable attorneys' fees and the costs of this action under 35 U.S.C. § 285; and
- (11) award Aventis Pharma any further and additional relief as this Court deems just and proper.

ASHBY & GEDDES

/s/ Steven J. Balick

Steven J. Balick (I.D. # 2114)
John G. Day (I.D. #2403)
Lauren E. Maguire (I.D. # 4261)
500 Delaware Avenue, 8th Fl.
P.O. Box 1150
Wilmington, Delaware 19899
Tel: (302) 654-1888

Attorneys for Plaintiff Aventis Pharma S.A.

Of Counsel:

James B. Monroe
Paul W. Browning
Kakoli Caprihan
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
901 New York Ave., N.W.
Washington, DC 20001
Tel.: (202) 408-4000

Dated: September 14, 2007

EXHIBIT A



US005565427A

United States Patent [19]

Freudenberg

[11] **Patent Number:** **5,565,427**
 [45] **Date of Patent:** **Oct. 15, 1996**

[54] **STABILIZED FACTOR VIII PREPARATIONS**

[75] Inventor: **Wilfried Freudenberg**,
Cölbe-Schönstadt, Germany

[73] Assignee: **Behringwerke Aktiengesellschaft**,
Marburg, Germany

[21] Appl. No.: **235,241**

[22] Filed: **Apr. 29, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 82,911, Jun. 29, 1993, abandoned, which is a continuation of Ser. No. 864,610, Apr. 7, 1992, abandoned.

[30] **Foreign Application Priority Data**

Apr. 9, 1991 [DE] Germany 41 11 393.4

[51] **Int. Cl.⁶** **A61K 35/14**; C07K 1/00;
C07K 14/00

[52] **U.S. Cl.** **514/12**; 514/21; 530/383

[58] **Field of Search** 530/383; 514/12,
514/21

[56] **References Cited****U.S. PATENT DOCUMENTS**

4,650,858	3/1987	Rasmussen et al.	530/383
4,743,680	5/1988	Mathews et al.	530/413
5,110,907	5/1992	Kosow et al.	530/413

OTHER PUBLICATIONS

H. Schwinn et al., Drug. Res., vol. 39 (II.), No. 10: 1302-1305 (1989).

Meyers, R. et al., "Large Scale Preparation of a Highly Purified Solvent-Detergent Treated Factor VIII Concentrate," VOX Sang. vol. 60, pp. 141-147 (1991).

Primary Examiner—Elizabeth C. Weimar

Assistant Examiner—P. Lynn Touzeau

Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

[57] **ABSTRACT**

The invention relates to stabilized solutions with F VIII coagulation activity, to a process for the preparation thereof and to the use thereof.

13 Claims, No Drawings

5,565,427

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STABILIZED FACTOR VIII PREPARATIONS

This application is a continuation of application Ser. No. 08/082,911 filed Jun. 29, 1993, now abandoned, which is a continuation of application Ser. No. 07/864,610, filed Apr. 7, 1992, abandoned.

The invention relates to stabilized solutions with F VIII coagulation activity, to a process for the preparation thereof and to the use thereof.

Coagulation factor VIII:C (F VIII:C) is a plasma protein and essential for the process of the intrinsic pathway of blood coagulation. A deficiency or a defect in blood coagulation factor VIII:C results in a life-threatening disturbance of blood coagulation, hemophilia A. Concentrates of F VIII:C from human plasma or genetically engineered F VIII:C are employed for the therapy of hemophilia A.

These F VIII products differ in respect of their purity, i.e. the presence of proteins which do not have coagulation activity in addition to the active substance F VIII:C. A F VIII which has more than 1000 U/mg before stabilization with albumin is called very high purity F VIII (VHP F VIII:C) (WHO, Expert Committee on Biological Standardization).

Such VHP F VIII:C have potential advantages in the treatment of hemophilia. These are the freedom from viruses and a very small content of foreign protein, which means less stress on the immune system of the patients after administration of these concentrates. The advantage which is possible per se, of less stress on the immune system of a hemophiliac patient by administration of a F VIII preparation with high specific activity, is, however, cancelled out by addition of high albumin concentrations to the highly purified product in order to stabilize the VHP F VIII. This addition of albumin means that the highly purified F VIII concentrates reach specific activities of only 3–10 U/mg in the final formulation thereof.

Although addition of albumin entails only a slight risk with respect to virus safety, it has to be borne in mind, however, that with albumin whose purity averages 95% once again unwanted concomitant proteins are administered to the patient and may stress his immune system.

High purity F VIII product: which dispense with addition of albumin for stabilization of F VIII are known (Schwinn, Smith & Wolter, Drug. Res. 39 (1989), 1302). These products reach specific activities of about 100 U/mg of protein. Based on a maximum achievable F VIII activity of about 5000 U/mg, this means that only about 2% of the protein content of these preparations comprises F VIII:C protein. It is to be assumed in this case that this 2% F VIII:C is stabilized by the 98% concomitant proteins, because a large part of these concomitant proteins is likely to comprise von Willebrand Factor (vWF). It is known that von Willebrand Factor has a stabilizing action on F VIII:C.

The situation is different with very high purity products which have specific activities which, before albumin stabilization, are usually more than 25 times higher than for high purity products, and the vWF content thereof is very low. This low vWF content is no longer able to ensure adequate F VIII stabilization so that the F VIII activity in solutions which are not stabilized with albumin rapidly decreases.

The object of the present invention was therefore to provide a process which makes it possible to prepare a highly concentrated, physiologically tolerated solution of a VHP F VIII:C product, which solution requires no addition of proteins for stabilization.

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This object is achieved according to the invention by adding an amino acid or one of its salts, derivatives or homologs to a VHP F VIII:C preparation. It is possible to add L- and/or D-amino acids. Particular suitable are arginine, lysine, ornithine, guanidinoacetic acid or others whose common feature is a basic group in the form of an amino and/or guanidino group.

The invention therefore relates to a solution with factor VIII:C activity containing an amino acid or one of its salts or derivatives and, where appropriate, a detergent or an organic polymer.

Preferred embodiments are:

- a solution wherein the amino acid is a natural amino acid;
- a solution wherein the amino acid is a basic amino acid;
- a solution which contains arginine and glycine;
- a solution wherein the concentration of the amino acid is 0.001 to 1 mol/l;

- a solution which additionally contains an organic polymer or a nonionic detergent;

- a solution wherein the F VIII:C activity derives from human factor VIII in its form which occurs in plasma or from a genetically engineered factor VIII:C or a derivative of these;

- and a solution wherein the specific F VIII:C activity is at least 1000 IU/mg.

Improved stabilization is achieved by combination of amino acids or their derivatives or with a nonionic detergent such as ^RPolysorbate 20 or ^RPolysorbate 80 or an organic polymer such as polyethylene glycol 1500.

A combination of the amino acids arginine and glycine, preferably 0.01 to 1 mol/l, with the nonionic detergent ^RTween 80, preferably 0.001 to 0.5% (v/v), and with a neutral sugar such as sucrose, preferably 0.1 to 10%, has proven particularly suitable for the preparation of a stable, albumin-free VHP F VIII:C solution.

The pH of a solution of this type is adjusted to between pH 5.5 and 8.5, preferably between pH 6.5 and 7.5, by means of an organic acid, preferably 10% strength acetic acid.

The invention also relates to a pharmaceutical containing a solution of this type. Besides a solution of this type, this pharmaceutical can contain customary, pharmaceutically compatible, stabilizing and/or buffering substances, especially a carbohydrate.

The invention likewise relates to a process for the preparation of a solution of this type, wherein an amino acid or one of its salts or derivatives and, where appropriate, an organic polymer or a detergent is added to a solution with factor VIII:C activity.

The advantageous effect of the process according to the invention can be shown, for example, for a F VIII:C preparation which has been purified by chromatography on monoclonal anti-F VIII:C antibodies, it being possible for the F VIII:C to be both obtained from plasma and genetically engineered, for example in CHO (Chinese Hamster Ovary) cells. This entails, for example, equal parts of a solution of the abovementioned substances being added to the eluate from the monoclonal antibody column, and subsequently the latter being dialyzed against this solution. The stabilized F VIII:C preparation obtained in this way can be sterilized by filtration and bottled with low method-related losses. A lyophilizate of this preparation obtained in this way has unchanged high F VIII:C activities after dissolution.

It is possible with the process according to the invention to prepare a VHP F VIII:C preparation whose specific volume-based activity is at least 200 IU/ml, with a specific activity of more than 2000 IU/mg. This concentration ensures that there are no problems with manipulation owing to the need to administer small volumes.

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A preparation of this type does not need further stabilization by proteins, which avoids the risk of virus contamination. At the same time, the reduction in the high protein load means a considerable reduction in the stress on the immune system of the patient due to the addition of the albumin, which is unnecessary for the medicinal action, and of the unwanted impurities contained therein.

Since physiologically tolerated substances are added for the stabilization, no intolerance reactions occur on administration of the solution according to the invention.

EXAMPLE 1

Two VHP F VIII:C preparations were prepared, both by means of affinity chromatography on monoclonal anti-vWF Ig (method of Fulcher & Zimmermann PNAS (1982), 79, 1649) and dissociation of the vWF/F VIII:C complex by solution with a CaCl_2 concentration of 300 mM in 0.1 M acetate, 0.1 M lysine, pH 6.8 (eluate I), and by means of chromatography on monoclonal anti-F VIII:C Ig and elution of the F VIII:C by 50% ethylene glycol in 0.1 M acetate, 0.1 M lysine, pH 6.8 (eluate II). The specific F VIII:C activity determined in eluate I was 2500 IU/mg and 419 IU/ml, and in eluate II was 3280 IU/mg and 454 IU/ml. The two eluates were divided in each case. To one portion in each case was added in the ratio 1:1 by volume a 1% strength human albumin solution in 0.75% sucrose, 3% glycine and 0.1 mol/l NaCl (eluate I_{HSA}, eluate II_{HSA}). The stabilization buffer (0.75% sucrose, 3% glycine, 3% arginine, 0.05% *r*-Tween 80, pH 6.8) was likewise added 1:1 to the other half in each case (eluate I_S, eluate II_S). The albumin-containing samples were dialyzed against 0.75% sucrose, 3% glycine, 0.1 mol/l NaCl, pH 6.8, and the others against stabilization buffer. Dialysis was carried out at 4° C. for 16 hours with 1000-fold volume change. The F VIII:C activities were measured before and after the dialysis. Table 1 shows the F VIII:C activity in % relative to the total F VIII:C activity in the particular sample before dialysis.

TABLE 1

Eluate I _{HSA}	Eluate I _S	Eluate II _{HSA}	Eluate II _S
92	94	94	93

The results show that stabilization of the VHP F VIII:C eluates by means of the stabilization solution according to the invention is achieved irrespective of the preparation method and to the same extent as by addition of albumin.

EXAMPLE 2

An F VIII:C eluate with a specific F VIII:C activity of 3860 IU/mg of protein and 462 IU/ml was obtained after immunoaffinity chromatography on monoclonal anti-F VIII:C antibodies. Various stabilization solutions were added to this in the ratio 1:1 by volume, and it was dialyzed against the relevant stabilization solution as described in Example 1. A pH of 6.8 was adjusted in all solutions where appropriate with 10% acetic acid.

The following stabilization solutions were employed:

- I. 0.75% sucrose, 0.4 M glycine, 0.15 M sodium chloride
- II. 0.01M sodium citrate, 0.08 M glycine, 0.016 M lysine, 0.0025 M calcium chloride, 0.4 M sodium chloride

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III. 1% sucrose, 0.14 M arginine, 0.1M sodium chloride

IV. 1% sucrose, 0.4 M glycine, 0.14 M arginine, 0.1M sodium chloride, 0.05% Tween 80

The F VIII:C activity was determined before and after the dialysis. In Table 2 the F VIII:C activity after dialysis is plotted in % relative to the relevant activity before dialysis.

TABLE 2

Mixture	I	II	III	IV
F VIII:C activity after dialysis for 16 hours	39.3%	35.1%	82.4%	96.2%

The solutions employed under I and II can be employed for the stabilization of albumin-free HP F VIII products with specific F VIII:C activities of 100–200 IU/mg, dispensing with addition of albumin. Solutions III and IV are suitable for stabilization of VHP F VIII preparations with specific F VIII:C activities greater than 1000 IU/mg.

I claim:

1. A stabilized solution with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs and a detergent or an organic polymer, wherein the specific factor VIII:C activity is at least 1000 IU/mg.

2. A solution as claimed in claim 1, wherein the amino acid is a natural amino acid.

3. A solution as claimed in claim 1, wherein the amino acid is a basic amino acid.

4. A solution as claimed in claim 1, which contains arginine and glycine.

5. A solution as claimed in claim 1, wherein the concentration of the amino acid is 0.001 to 1 mol/l.

6. A solution as claimed in claim 1, which contains an organic polymer or a nonionic detergent.

7. A solution as claimed in claim 1, wherein the F VIII:C activity is derived (a) from human factor VIII in its form which occurs in plasma or (b) from a genetically engineered factor VIII:C or (C) from a homolog of (a) or (b).

8. A pharmaceutical containing a solution as claimed in claim 1.

9. A pharmaceutical as claimed in claim 8 further containing pharmaceutically compatible, stabilizing or buffering substances.

10. A pharmaceutical as claimed in claim 9, which contains a carbohydrate.

11. A process for the preparation of a stable factor VIII:C solution which comprises adding an amino acid or one of its salts or homologs and an organic polymer or a detergent to a solution with factor VII I:C activity, wherein the specific factor VIII:C activity is at least 1000 IU/mg.

12. A stabilized solution as claimed in claim 1 containing an amino acid or one of its salts or homologs and an organic polymer, wherein the amino acid is arginine or glycine and the organic polymer is polyethylene glycol.

13. A stabilized solution as claimed in claim 1 containing an amino acid or one of its salts or homologs and a detergent, wherein the amino acid is arginine or glycine and the detergent is polyoxyethylene sorbitan mono-oleate.

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EXHIBIT B



US005565427C1

(12) **REEXAMINATION CERTIFICATE (4618th)**
United States Patent
Freudenberg

(10) Number: **US 5,565,427 C1**
 (45) Certificate Issued: **Jul. 23, 2002**

(54) **STABILIZED FACTOR VIII PREPARATIONS**

(75) Inventor: **Wilfried Freudenberg,**
 Cölbe-Schönstadt (DE)

(73) Assignee: **Aventis Behring GmbH, Marburg (DE)**

Reexamination Request:

No. 90/006,025, May 30, 2001

Reexamination Certificate for:

Patent No.: **5,565,427**
 Issued: **Oct. 15, 1996**
 Appl. No.: **08/235,241**
 Filed: **Apr. 29, 1994**

Certificate of Correction issued Feb. 18, 1997.

Related U.S. Application Data

(63) Continuation of application No. 08/082,911, filed on Jun. 29, 1993, now abandoned, which is a continuation of application No. 07/864,610, filed on Apr. 7, 1992, now abandoned.

(30) **Foreign Application Priority Data**

Apr. 9, 1991 (DE) 41 11 393

(51) Int. Cl.⁷ A61K 35/14; C07K 1/00; C07K 14/00

(52) U.S. Cl. 514/12; 514/21; 530/383

(58) Field of Search 514/12, 21; 530/383

(56) **References Cited****U.S. PATENT DOCUMENTS**

4,440,679 A * 4/1984 Fernandes et al. 530/363
 4,446,134 A * 5/1984 Naito et al. 514/2
 4,495,175 A * 1/1985 Chavin et al. 530/383
 4,543,210 A * 9/1985 Mitra et al. 530/383
 4,623,717 A * 11/1986 Fernandes et al. 530/380
 4,650,858 A * 3/1987 Rasmussen et al. 530/383
 4,743,680 A * 5/1988 Mathews et al. 530/383
 4,749,780 A * 6/1988 Andersson et al. 530/383
 4,795,806 A * 1/1989 Brown et al. 530/383

4,857,635 A * 8/1989 Zimmerman et al. 530/383
 4,877,608 A * 10/1989 Lee et al. 424/85.8
 5,110,907 A * 5/1992 Kosow et al. 530/383
 5,328,694 A * 7/1994 Schwinn 424/423
 5,565,427 A * 10/1996 Freudenberg 514/12
 5,605,884 A * 2/1997 Lee et al. 514/8
 5,760,183 A * 6/1998 Dazey et al. 530/383

FOREIGN PATENT DOCUMENTS

AU 60150/90 * 2/1991
 EP 123 945 * 11/1984
 EP 315 968 * 5/1989
 EP 383 645 * 8/1990
 EP 468 181 * 1/1992
 GB 941019 * 11/1963
 WO 91/10439 * 7/1991

OTHER PUBLICATIONS

Myers et al. Large-Scale Preparation of a Highly Purified Solvent-Detergent Treated Factor VIII Concentrate. Vox Sang. 1991, vol. 60, pp. 141-147.*

Fay et al. Purification and characterization of a highly purified human factor VIII consisting of a single type of polypeptide chain. Proc. Natl. Acad. Sci. USA, Dec. 1982, vol. 79, pp. 7200-7204.*

Fulcher et al. Characterization of the human factor VIII procoagulant protein with a heterologous precipitating antibody. Proc. Natl. Acad. Sci. USA, Mar. 1982, vol. 79, pp. 1648-1652.*

Schwinn et al. Progress in Purification of Virus-inactivated Factor VIII Concentrates. Drug Res. 1989, vol. 39 (II), No. 10, pp. 1302-1305.*

Lewis, Sr. Hawley's Condensed Chemical Dictionary, Twelfth Edition. 1993, pp. 53, 357, 606, 936, 1020.*

* cited by examiner

Primary Examiner—Jeffrey E. Russel

(57) **ABSTRACT**

The invention relates to stabilized solutions with F VIII coagulation activity, to a process for the preparation thereof and to the use thereof.

US 5,565,427 C1

1
REEXAMINATION CERTIFICATE
ISSUED UNDER 35 U.S.C. 307

NO AMENDMENTS HAVE BEEN MADE TO
THE PATENT

2
AS A RESULT OF REEXAMINATION, IT HAS BEEN
DETERMINED THAT:

The patentability of claims 1-13 is confirmed.

* * * * *

2006/09/14 15:20:00

EXHIBIT C

(12) **EX PARTE REEXAMINATION CERTIFICATE (5561st)**
United States Patent
Freudenberg

(10) Number: **US 5,565,427 C2**
 (45) Certificate Issued: **Oct. 10, 2006**

(54) **STABILIZED FACTOR VIII PREPARATIONS**

(75) Inventor: **Wilfried Freudenberg,**
Cölbe-Schönstadt (DE)

(73) Assignee: **A. Nattermann und Cie GmbH,**
Cologne (DE)

Reexamination Request:

No. 90/006,823, Oct. 21, 2003

Reexamination Certificate for:

Patent No.: **5,565,427**
 Issued: **Oct. 15, 1996**
 Appl. No.: **08/235,241**
 Filed: **Apr. 29, 1994**

Reexamination Certificate C1 5,565,427 issued Jul. 23, 2002

Certificate of Correction issued Feb. 18, 1997.

Related U.S. Application Data

(63) Continuation of application No. 08/082,911, filed on Jun. 29, 1993, now abandoned, which is a continuation of application No. 07/864,610, filed on Apr. 7, 1992, now abandoned.

(30) **Foreign Application Priority Data**

Apr. 9, 1991 (DE) 41 11 393

(51) **Int. Cl.**

A61K 35/14 (2006.01)
C07K 1/00 (2006.01)
C07K 14/00 (2006.01)

(52) **U.S. Cl.** 514/12; 514/21; 530/383

(58) **Field of Classification Search** 514/12,
 514/21; 530/383

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,089,944 A	5/1978	Thomas	424/101
4,297,344 A	10/1981	Schwinn et al.	424/101
4,614,795 A	9/1986	Chavin et al.	530/383
4,758,657 A	7/1988	Farb et al.	530/383
4,981,951 A	1/1991	Tsay	530/383
5,043,428 A	8/1991	Heimbürger et al.	530/383
5,068,106 A	11/1991	Pâques et al.	424/94.3
5,424,401 A	6/1995	Heimbürger et al.	530/383

FOREIGN PATENT DOCUMENTS

EP	0 035 204 B1	9/1981
EP	0 286 323 B1	10/1988
EP	0 314 095	5/1989
EP	0 412 466 A2	8/1990
EP	0 410 207 *	1/1991
WO	WO 90/05140	5/1990

OTHER PUBLICATIONS

Oct. 4, 2004, Deposition Transcript and Exhibits of the Deposition of C. Einaudi.

Oct. 12, 2004, Deposition Transcript and Exhibits of the Deposition of J. Bennett.

Oct. 14, 2004, Deposition Transcript and Exhibits of the Deposition of H. Lauppe.

Oct. 15, 2004, Deposition Transcript and Exhibits of the Deposition of A. Groner.

Oct. 21, 2004, Deposition Transcript and Exhibits of the Deposition of W. Freudenberg.

Feb. 15, 2004, Letter to Judge Brody with exhibits.

Jul. 11, 2003, Transcript of Jul. 11, 2003 hearing.

Jul. 30, 2003, Plaintiffs' Response to Baxter's First Set of Interrogatories (Nos. 1-16) and Notice of Service.

Aug. 13, 2003, Plaintiffs' Objections and Responses to Baxter's First Set of Requests for Admission (Nos. 1-85) and Notice of Service.

Sep. 17, 2003, Highlighted Farb document submitted during the Sep. 17, 2003 hearing with Judge Sleet.

Sep. 17, 2003, Transcript of Sep. 17, 2003 hearing.

Oct. 1, 2003, Plaintiffs' Supplemental Response to Baxter's First Set of Interrogatories (Nos. 1-16) and Notice of Service.

Oct. 7, 2003, Letter from Balick to Judge Sleet.

Oct. 7, 2003, Letter from Rovner to Judge Sleet.

Oct. 10, 2003, Transcript of Oct. 10, 2003 hearing.

Jul. 30, 2003, Plaintiffs' Objections and Responses to Bayer's First Set of Interrogatories (Nos. 1-19) and Verification of Answers and Certificate of Service.

Aug. 4, 2003, Defendants' Responses to Plaintiffs' First Set of Interrogatories (Nos. 1-18) and Certificate of Service.

Aug. 4, 2003, Defendants' Responses to Plaintiffs' First Set of Requests for Admission (Nos. 1-13) and Certificate of Service.

Oct. 3, 2003, Plaintiffs' Objections and Responses to Bayer's First Set of Requests for Admission (Nos. 1-8) and Notice of Service.

Oct. 3, 2003, Plaintiffs' Objections and Responses to Bayer's Second Set of Interrogatories (Nos. 20-26) and Notice of Service.

Nov. 12, 2003, Plaintiffs' Motion to Dismiss All Claims and Counterclaims without Prejudice or, in the Alternative, Stay Proceedings Pending Reexamination of U.S. Pat. No. 5,565,427.

Nov. 21, 2003, Plaintiff's Opposition to Defendant's Motion for leave to file amended answer and counterclaims.

Mar. 22, 2004, Transcript of Motion before Judge Brody to stay or dismiss.

Mar. 30, 2004, ORDER.

Mar. 30, 2004, Bayer's subpoena of Finnegan-Henderson of documents in attached Schedule A.

Mar. 30, 2004, Defendant's Revised Notice of Deposition of A. Nattermann & Cie GmbH, Aventis Behring L.L.C. & Aventis Behring GmbH Pursuant to Rule 30(b)(6).

Apr. 2, 2004, Notice of Service of Subpoena on Finnegan-Henderson and Subpoena itself.

(Continued)

Primary Examiner—Kathleen M. Kerr

(57) **ABSTRACT**

The invention relates to stabilized solutions with F VIII coagulation activity, to a process for the preparation thereof and to the use thereof.

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OTHER PUBLICATIONS

May 3, 2004, Letter from T. Donaldson to T. Poche attaching Plaintiffs' objections and responses to Bayer's Mar. 30, 2004 Subpoena of Finnegan Henderson.

May 8, 2004, Order of May 8, 2004.

May 13, 2004, Order that Defendants' motion for summary judgment is DENIED without prejudice.

Jun. 1, 2004, ORDER memorializing parties agreement to complete depositions on or before Oct. 15, 2004.

Jun. 4, 2004, ORDER stating that Plaintiff's Motion to Stay and Plaintiff's Motion for Discovery are Denied as moot.

Sep. 27, 2004, Letter attaching copies of Subpoena of D. Farb, Notice of Services of Subpoena, Defendants' Notice of Deposition of Farb.

Sep. 27, 2004, Letter stating that Finnegan will be representing Dr. D. Farb at his deposition and will accept service on his behalf.

Sep. 28, 2004, Letter from T. Donaldson to T. Poche.

Oct. 21, 2004, Transcript of teleconference between Bayer, Aventis and Judge Brody re deposition of Dr. Freudenberg.

Feb. 16, 2005, Letter to Judge Brody.

Feb. 24, 2005, Letter to Judge Brody.

Mar. 4, 2005, Letter to the Court.

Mar. 10, 2005, Letter to the Court.

Mar. 11, 2005, Letter to Judge Brody.

Mar. 15, 2005, Letter to Judge Brody.

Mar. 16, 2005, Letter to Judge Brody.

Mar. 16, 2005, Copy of ORDER maintaining current stay pending the reexamination by the USPTO and requiring that parties keep the Court updated on its progress.

Derwent Abstract for WO 90/05140.

I. Scharrer, "Current status of a recombinant antihemophilic factor VIII clinical trial organized by Baxter," *Ann. Hematology*, 63: 172-176 (1991).

Order Granting Plaintiff's Motion for Discovery Under FED. R. CIV. P. 56(f).

Motion for Discovery Under FED. R. CIV. P. 56(f) on behalf of Plaintiffs filed Nov. 24, 2003.

Redacted Copy of Plaintiff's Memorandum in Support of Motion for Discovery Under FED. R. CIV. P. 56(f) filed Nov. 24, 2003, with attached Exhibits 1-16.

Order Denying Bayer's Motion for Summary Judgment of Noninfringement.

Redacted copy of Plaintiff's Opposition to Defendant's Motion for Summary Judgment of Noninfringement filed Nov. 24, 2003, with attached Exhibits 1-9.

Order Dismissing All Claims and Counterclaims Without Prejudice.

Order Staying Any Further Proceedings Pending Outcome of Reexamination of U.S. Pat. No. 5,565,427.

Plaintiffs' Memorandum of Law in Support of Its Motion to Dismiss All Claims and Counterclaims Without Prejudice or, in the Alternative, Stay Proceedings Pending Reexamination of U.S. Pat. No. 5,565,427 (Exhibits 1-10) filed Jan. 16, 2004.

Plaintiff's Answer to First Amended Counterclaims, filed Dec. 23, 2003.

Transcript of Dec. 1, 2003, hearing before the Honorable Anita B. Brody in Civil Action No. 03-2268 in the United States District Court for the Eastern District of Pennsylvania.

Bayer's Opposition to Plaintiffs' Motion to Dismiss All Claims and Counterclaims Without Prejudice or, in the Alternative, Stay Proceedings Pending Reexamination of U.S. Pat. No. 5,565,427 (with Exhibits), filed Jan. 30, 2004. Plaintiffs' Memorandum of Law in Opposition to Defendants' Motion For a Rule 54(b) Declaratory Judgment Regarding Aventis Behring's State Court Action (with Exhibits), filed Feb. 9, 2004.

Plaintiffs' Reply Memorandum of Law in Support of its Motion to Dismiss All Claims and Counterclaims Without Prejudice or, in the Alternative, Stay Proceedings Pending Reexamination of U.S. Pat. No. 5,565,427 (with Exhibits), filed Feb. 13, 2004.

Defendants' Reply to Plaintiffs' Memorandum of Law in Opposition to Defendants' Motion For Rule 54(b) Declaratory Judgment Regarding Aventis Behring's State Court Action (with Exhibits), filed Feb. 16, 2003.

Order dated Feb. 19, 2004 in Civ. A. No. 03-2268 (*Nattermann v. Bayer* litigation).

Letter from Bayer's counsel to Honorable Anita B. Brody regarding Protective Order (with Exhibits) dated Mar. 12, 2004.

Letter from Nattermann's counsel to Honorable Anita B. Brody regarding Protective Order dated Mar. 17, 2004.

Order dated Nov. 25, 2003 in Civ. A. No. 03-2268 (*Nattermann v. Bayer* litigation).

Bayer's Opposition to Plaintiffs' Motion To Dismiss All Claims And Counterclaims Without Prejudice or, in the Alternative, Stay Proceedings Pending Reexamination (with Exhibits), filed Nov. 26, 2003.

Defendants' First Amended Answer And Counterclaims, filed Nov. 26, 2003.

Transcript of Hearing Held on Dec. 1, 2003 in Civ. A. No. 03-2268 (*Nattermann v. Bayer* litigation).

Plaintiffs' Answer to First Amended Counterclaim, filed Dec. 23, 2003.

Letter from Bayer's Counsel to Honorable Anita B. Brody dated Jan. 7, 2004, submitted in Civ. A. No. 03-2268 (with Exhibits).

Letter from Nattermann's counsel to Honorable Anita B. Brody dated Jan. 9, 2004, submitted in Civ. A. No. 03-2268 (with Exhibits).

Plaintiffs' Motion To Dismiss All Claims And Counterclaims Without Prejudice Or, In The Alternative, Stay Proceedings Pending Reexamination Of U.S. Pat. No. 5,565,527 (with Order and Exhibits), filed Jan. 16, 2004.

Letter from Bayer's counsel to Honorable Anita B. Brody forwarding Stipulated Protective Order and copy of Stipulated Protective Order, dated Jan. 21, 2004.

Transcript of Jan. 12, 2004 hearing in the Civ. A. No. 03-2268 (*Nattermann v. Bayer* litigation).

Bayer's Motion For Declaratory Judgment of Waiver of Plaintiff's Compulsory Counterclaims (with Exhibits), filed Jan. 26, 2004.

Order dated Jan. 29, 2004 in Civ. A. No. 03-2268 (*Nattermann v. Bayer* litigation).

Arakawa, Tsutomu et al., "Stabilization of Protein Structure by Sugars," *Biochemistry*, vol. 21: 6536-6544 (1982).

Berntorp, Erik, et al., "Hepatitis C Virus Transmission by Monoclonal Antibody Purified Factor VIII Concentrate," *The Lancet*, vol. 335: 1531-1532 (1990).

Bray, Gordon L., "Recent Advances in the Preparation of Plasma-Derived and Recombinant Coagulation Factor VIII" *The Journal of Pediatrics*: 503-507 (1990).

Tootill, E., "The Facts on File Dictionary of Biology," Revised and Expanded Edition, pp. 44; 293.

Kernoff, Peter B. A., "Hepatitis and Factor VIII Concentrates," *Seminars in Hematology*, vol. 25:2, Suppl. 1: 8-13 (1988).

Lee, James C. et al., "The Stabilization of Proteins by Sucrose," *The Journal of Biological Chemistry*, vol. 256: (14) 7193-7201 (1981).

Lusher, Jeanne M. et al., "Viral Safety and Inhibitor Development Associated With Factor VIII Ultra-Purified From Plasma in Hemophiliacs Previously Unexposed to Factor VIII Concentrates," *Seminars in Hematology*, vol. 27:2, Suppl. 2: 1-7 (1990).

Budavari, Susan et al. (eds.), "The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals," p. 1401 (1989).

Pierce, Glen F. et al., "The Use of Purified Clotting Factor Concentrates in Hemophilia. Influence of Viral Safety, Cost, and Supply on Therapy," *JAMA*, vol. 261:23, (1989).

Stryer, Lubert, "Biochemistry Third Edition," pp. 16-21 (1988).

A. Munoz et al., "A randomized hemodynamic comparison of intravenous amiodarone with and without Tween 80," *European Heart Journal*, vol. 9: 142-148 (1988).

Complaint for Patent Infringement filed by A. Nattermann & Cie GmbH et al. against Baxter Healthcare Corp. in the District Court for the District of Delaware (Apr. 11, 2003).

Answer and Counterclaim for Declaratory Judgment filed by Baxter Healthcare Corp. in the District Court for the District of Delaware (May 27, 2003).

Reply of Counterclaim filed by A. Nattermann & Cie GmbH et al. in the District Court for the District of Delaware (Jun. 18, 2003).

Defendants' Answer and Counterclaims filed by Bayer Corp. et al., in the District Court for the Eastern District of Pennsylvania (May 1, 2003).

Answer to Counterclaims filed by A. Nattermann & Cie GmbH et al. in the District Court for the Eastern District of Pennsylvania (May 21, 2003).

Defendants' Motion for Summary Judgment of Noninfringement (with attachments), filed by Bayer Corp. et al., in the District Court for the Eastern District of Pennsylvania (Oct. 10, 2003).

Memorandum in Support of Defendants' Motion for Summary Judgment of Noninfringement (with attachments), filed by Bayer Corp. et al., in the District Court for the Eastern District of Pennsylvania (Oct. 10, 2003).

Bayer Corporations's and Bayer Healthcare LLC's Motion for Leave to File Defendants' First Amended Answer and Counterclaims filed in the District Court for the Eastern District of Pennsylvania (with attachments) (Oct. 14, 2003).

Bayer Corporations's and Bayer Healthcare LLC's Memorandum in Support of Their Motion for Leave to File Defendants' First Amended Answer and Counterclaims filed in the District Court for the Eastern District of Pennsylvania (with attachments) (Oct. 14, 2003).

* cited by examiner

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**EX PARTE
REEXAMINATION CERTIFICATE
ISSUED UNDER 35 U.S.C. 307**

THE PATENT IS HEREBY AMENDED AS
INDICATED BELOW.

Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claim 11 is confirmed.

Claim 1 is cancelled.

Claims 2-8, 10, 12 and 13 are determined to be patentable as amended.

Claim 9, dependent on an amended claim, is determined to be patentable.

New claims 14-23 are added and determined to be patentable.

2. A solution as claimed in claim [1] 15, wherein the amino acid is a natural amino acid.

3. A solution as claimed in claim [1] 15, wherein the amino acid is a basic amino acid.

4. *A stabilized solution [as claimed in claim 1, which] with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs and a detergent or an organic polymer, wherein the specific factor VIII:C activity is at least 1000 IU/mg and wherein the stabilized solution contains arginine and glycine.*

5. A solution as claimed in claim [1] 15, wherein the concentration of the amino acid is 0.001 to 1 mol/l.

6. A solution as claimed in claim [1] 15, which contains an organic polymer or a nonionic detergent.

7. A solution as claimed in claim [1] 15, wherein the F VIII:C activity is derived (a) from human factor VIII in its form which occurs in plasma or (b) from a genetically engineered factor VIII:C or (c) from a homolog of (a) or (b).

8. A pharmaceutical containing a solution as claimed in claim [1] 14.

10. A pharmaceutical [as claimed in claim 9] which contains *a stabilized solution with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs, a detergent or an organic polymer, and a carbohydrate wherein the specific factor VIII:C activity is at least 1000 IU/mg, and further containing pharmaceutically compatible, stabilizing or buffering substances.*

12. A stabilized solution [as claimed in claim 1] with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs and an organic polymer, wherein the specific factor VIII:C activity is at least 1000

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IU/mg, and wherein the amino acid is arginine or glycine and the organic polymer is polyethylene glycol.

13. A stabilized solution as claimed in claim [1] 15, containing an amino acid or one of its salts or homologs and a detergent, wherein the amino acid is arginine or glycine and the organic detergent is polyoxyethylene sorbitan monooleate.

14. *A stabilized solution with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs and a detergent or organic polymer, wherein the specific factor VIII:C activity is at least 2000 IU/mg.*

15. *A stabilized solution with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs, a detergent or organic polymer, and a carbohydrate, wherein the specific factor VIII:C activity is at least 1000 IU/mg.*

16. *A stabilized solution with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs, a detergent or organic polymer, and a carbohydrate, wherein the specific factor VIII:C activity is at least 2000 IU/mg.*

17. *A stabilized solution with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs, a detergent or organic polymer, and a carbohydrate, wherein the specific factor VIII:C activity is at least 3280 IU/mg.*

18. *A stabilized solution with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs, a detergent or organic polymer, and a carbohydrate, wherein the specific factor VIII:C activity is at least 2000 IU/mg and wherein the stabilized solution with factor VIII:C activity does not contain albumin.*

19. *A stabilized solution with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs, a detergent or organic polymer, and a carbohydrate, wherein after lyophilization and reconstitution, the specific factor VIII:C activity is at least 2000 IU/mg.*

20. A solution as claimed in claim 7, wherein the factor VIII:C activity is derived from a genetically engineered factor VIII:C.

21. *A stabilized solution with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs, a detergent or organic polymer, wherein the specific factor VIII:C activity is at least 1000 IU/mg and wherein the potency of the stabilized factor VIII:C solution is at least 200 IU/ml.*

22. *A stabilized solution with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs, a detergent or organic polymer, and a carbohydrate, wherein the specific factor VIII:C activity is at least 2000 IU/mg and wherein the potency of the stabilized factor VIII:C solution is at least 200 IU/ml.*

23. *A stabilized solution with factor VIII:C activity containing factor VIII:C, an amino acid or one of its salts or homologs and a detergent or an organic polymer, wherein the specific factor VIII:C activity is at least 1000 IU/mg and wherein the concentration of detergent is from 0.001 to 0.05% w/v.*

* * * * *

EXHIBIT D



Baxter International Inc.
One Baxter Parkway
Deerfield, IL 60015

FOR IMMEDIATE RELEASE

Media Contact:

Amy Cynkar, (847) 940-5166

Investor Contacts:

Mary Kay Ladone, (847) 948-3371

Clare Sullivan, (847) 948-3085

**BAXTER RECEIVES FDA APPROVAL FOR ULTRA-HIGH
DOSAGE STRENGTH OF ADVATE FOR HEMOPHILIA A**

New 2000 IU Dosage Strength Increases Ease of Use for People with Hemophilia

DEERFIELD, Ill., May 9, 2006 – Baxter Healthcare Corporation today announced that the U.S. Food and Drug Administration (FDA) has approved a new 2000 IU (5mL) Ultra-High dosage of ADVATE[®] [Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method (rAHF-PFM)], the only therapy free of blood-based additives, used for the prevention and control of bleeding episodes in people with hemophilia A. The new Ultra-High dosage strength vial makes it easier for people requiring higher doses to administer ADVATE by reducing both the infusion volume of drug solution and the storage space. The therapy will be available to patients in the United States by the end of May.

“It’s always difficult to fit infusing into my daily schedule,” said Seth Rye, a 21-year-old hemophilia A patient. “With its shorter infusion time and faster and easier mixing, the Ultra-High dosage strength of ADVATE allows me more time to focus on the activities I enjoy, like swimming.”

As each person with hemophilia has different needs when it comes to their infusions, it is important for them to have a variety of dosage strengths from which to choose. With the approval of the Ultra-High dosage strength, ADVATE is now the only factor VIII therapy to offer people with hemophilia A in the United States five

**BAXTER RECEIVES FDA APPROVAL FOR ULTRA-HIGH DOSAGE STRENGTH OF
ADVATE FOR HEMOPHILIA A – PAGE 2**

different dosage strengths: Low (250 IU), Medium (500 IU), High (1000 IU), Super-High (1500 IU) and Ultra-High (2000 IU).

“We heard from the community that there was a need for more choices in dosage strengths for hemophilia therapies,” said Joy Amundson, president, Baxter's BioScience business. “Therefore, we are proud to offer the Ultra-High dosage strength of ADVATE, providing patients with one more reason to choose ADVATE, the therapy people with hemophilia have come to rely on.”

Since its introduction in 2003, ADVATE is the therapy more patients are choosing every day. With over one billion units of ADVATE distributed, ADVATE has been proven to be safe and effective in both clinical studies and in the real world.

About ADVATE

ADVATE is currently approved for use in the United States, Australia and 14 countries in the European Union.

ADVATE is indicated in hemophilia A (classical hemophilia) for the prevention and control of bleeding episodes. Infused directly into the bloodstream, ADVATE works by temporarily raising the level of factor VIII in the blood, thus allowing the body's blood clotting process to properly function. ADVATE is the only recombinant factor VIII therapy processed without blood or blood additives, including human albumin or other plasma protein additives.

ADVATE is also indicated in the perioperative management of patients with hemophilia A. ADVATE is not indicated for the treatment of von Willebrand's disease.

ADVATE should be administered cautiously in patients with previous hypersensitivity to constituents of factor VIII preparations or known sensitivity to mouse or hamster proteins.

The most common related adverse reactions observed during the ADVATE clinical studies include: strange taste in mouth, headache, dizziness and flushing. The formation of inhibitors has been observed with all factor VIII concentrates, including ADVATE.

For more information on ADVATE including full prescribing information, please visit www.advate.com.

**BAXTER RECEIVES FDA APPROVAL FOR ULTRA-HIGH DOSAGE STRENGTH OF
ADVATE FOR HEMOPHILIA A – PAGE 3**

About hemophilia A

People with hemophilia A do not produce adequate amounts of factor VIII, which is necessary for blood to effectively clot. If untreated, patients with severe hemophilia A have a greatly reduced life expectancy. According to the World Health Organization, more than 400,000 people in the world have hemophilia, corresponding to a prevalence of 15 to 20 in every 100,000 males born worldwide.

About Baxter

Baxter Healthcare Corporation is the principal U.S. operating subsidiary of Baxter International Inc. (NYSE:BAX). Baxter International Inc., through its subsidiaries, assists healthcare professionals and their patients with the treatment of complex medical conditions, including cancer, hemophilia, immune disorders, kidney disease and trauma. The company applies its expertise in medical devices, pharmaceuticals and biotechnology to make a meaningful difference in patients' lives.

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EXHIBIT E

Baxter International Inc.
One Baxter Parkway
Deerfield, IL 60015



FOR IMMEDIATE RELEASE

Media Contact:

Christopher Bona, (847) 948-2815

Deborah Spak, (847) 948-2349

Investor Contacts:

Mary Kay Ladone, (847) 948-3371

Clare Trachtman, (847) 948-3085

**BAXTER RECEIVES FDA APPROVAL FOR 3000 IU DOSAGE STRENGTH
OF ADVATE® FOR HEMOPHILIA A**

New 3000 IU Dosage Strength Saves Time for People with Hemophilia A

DEERFIELD, Ill., July 10, 2007 – Baxter Healthcare Corporation today announced that the U.S. Food and Drug Administration (FDA) has approved a new 3000 IU (5mL) dosage strength of ADVATE® [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method]. ADVATE is used for the prevention and control of bleeding episodes in people with hemophilia A and is the only factor VIII therapy free of blood-based additives. The new 3000 IU dosage strength vial makes it easier and faster for people requiring higher doses to administer ADVATE by decreasing the number of vials needed and reducing their total infusion volume. The ADVATE 3000 IU vial is also packaged with BAXJECT II for faster and easier mixing, as compared to original BAXJECT and needles. The dosage strength will be available to patients in the United States beginning in August 2007.

“The 3000 IU is ideal for me,” said Seth Rye, a patient with hemophilia A. “I now only have to use one vial to dose myself, and if you combine the 3000 IU with BAXJECT II, I’ve reduced my usual treatment time in half which is great.”

As each person with hemophilia A has different needs when it comes to infusions, it is important to have a variety of dosage strengths from which to choose. With the approval of the 3000 IU (5mL) dosage strength, ADVATE is the only factor VIII therapy to offer people with hemophilia A in the United States such a broad selection of dosage strengths: 250 IU, 500 IU,

1000 IU, 1500 IU, 2000 IU and 3000 IU.

“The new 3000 IU dosage strength vial will offer people with hemophilia A more flexibility in incorporating ADVATE into their therapeutic routines,” said Larry Guiheen, President, North America region, Baxter Bioscience. “Baxter is committed to expanding the ADVATE product line in order to streamline the process of infusion for patients, allowing it to fit more easily into their lives.”

Since its introduction in 2003, ADVATE is the therapy more patients are choosing every day*. With over two billion units of ADVATE distributed worldwide, ADVATE has been shown to be safe and effective in both clinical studies and in the real world.

The full marketing approval of ADVATE 3000 IU is anticipated in Europe in 2008.

About ADVATE

ADVATE is currently approved for use in the United States, Canada, Australia, Japan and in Europe.

ADVATE is indicated in hemophilia A (classical hemophilia) for the prevention and control of bleeding episodes and for perioperative management. ADVATE is not indicated for the treatment of von Willebrand disease. Infused directly into the bloodstream, ADVATE works by temporarily raising the level of factor VIII in the blood, thus allowing the body's blood clotting process to properly function. ADVATE is the only recombinant factor VIII therapy processed without blood or blood additives, including human albumin or other plasma protein additives.

ADVATE should be administered cautiously in patients with previous hypersensitivity to constituents of factor VIII preparations or known sensitivity to mouse or hamster proteins. The most common related adverse reactions observed during the ADVATE clinical studies include: strange taste in mouth, headache, dizziness and flushing.

Patients and caregivers in the United States can obtain more information on ADVATE, including full Prescribing Information at www.ADVATE.com.

BAXTER RECEIVES FDA APPROVAL FOR 3000 IU DOSAGE STRENGTH OF ADVATE® FOR HEMOPHILIA A – Page 3

About BAXJECT II

The BAXJECT II device is intended for use with a single vial of product and is for single use only. Therefore, reconstituting and withdrawing a second vial into the syringe requires a second BAXJECT II device. Rx only. For safe and proper use of this device, please refer to the Instructions for Use at www.BAXJECTII.com.

About hemophilia A

People with hemophilia A do not produce adequate amounts of factor VIII, which is necessary for blood to effectively clot. If untreated, patients with severe hemophilia A have a greatly reduced life expectancy. According to the World Health Organization, more than 400,000 people in the world have hemophilia, corresponding to a prevalence of 15 to 20 in every 100,000 males born worldwide.

Baxter Research and Development

Baxter focuses its scientific resources and leverages strategic collaborations to advance the management of hemophilia and blood clotting disorders. Building on its history of innovation, the company is developing therapies to provide less invasive dosing techniques, require less frequent infusions, and/or reduce the potential for inhibitor formation, and improve the lives of people with bleeding disorders.

About Baxter

Baxter Healthcare Corporation is the principal U.S. operating subsidiary of Baxter International Inc. (NYSE:BAX). Baxter International Inc., through its subsidiaries, assists healthcare professionals and their patients with the treatment of complex medical conditions, including cancer, hemophilia, immune disorders, kidney disease and trauma. The company applies its expertise in medical devices, pharmaceuticals and biotechnology to make a meaningful difference in patients' lives.

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* Number of patients prescribed ADVATE is growing everyday as per provider database on file at Baxter Healthcare Corporation